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Election of June 1, 1998

The Examiner's withdrawal of the election of species requirements in Second Section 10, Section 13 and Section 16 of the March 30, 1998 Office Action (Paper No. 3) is acknowledged, with appreciation. In accordance with the Examiner's withdrawal of these election requirements, the Applicant adds new claims 26 and 27 to reintroduce the formerly provisionally non-elected species identified in Second Section 10; new claims 28 and 29 to reintroduce the formerly provisionally non-elected species identified in Section 13; and new claim 30 to reintroduce the formerly provisionally non-elected species identified in Section 16.

The Examiner indicated that the election of species in the other sections was made without traverse. However, the Applicant respectfully submits that the election of species required by Section 15 of the March 30, 1998 Office Action was made with traverse. See page 7, second full paragraph, of Applicant's June 1, 1998 Amendment in Response to Election Requirement. The Applicant elected that the orally fed antibody is (a) fed by itself as a powder form, and deleted the language claiming the orally fed antibody fed (b) as a liquid form, (c) as a compressed tablet, or (d) other type of pill/tablet like material.

Because the Examiner did not repeat the restriction of Section 15, the Applicant understands this election requirement to be withdrawn, so the Applicant added new claims 31 and 32, wherein it is reintroduced that the antibody is fed in liquid form, and as a compressed tablet, respectively. 37 C.F.R. § 1.143.

Oath/Declaration

In response to the Examiner's indication that the oath has not been submitted, the Applicant submits herewith a substitute combined Declaration/Power of Attorney. In the event any further documents are required in order to meet the Examiner's requirement in this regard, the Examiner is requested to contact the Applicant's undersigned attorney so that any further such documents can be prepared, executed if necessary, and filed.

Claim Rejections

35 U.S.C. § 112

The Examiner rejected claims 1-4, 8, 11, 14, 17-22 and 25 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as his invention. In response, the Applicant amended claim 1 by changing "decreasing fat absorption" to -- inhibiting lipase so as to reduce fat absorption --.

35 U.S.C. § 102(b)

The Examiner rejected claim 25 under 35 U.S.C. § 102(b) as being anticipated by Murase et al (Atherosclerosis, 1981, 39:293-300). The Applicant respectfully traverses the Examiner's rejection. While it was well known prior to Applicant's invention that pancreatic lipase regulates a biochemical process, namely the breakdown of dietary fat, in the gastrointestinal tract, the Murase et al. reference is concerned not with pancreatic lipase, but rather, with the role of hepatic triglyceride lipase (HTGL) in plasma lipoprotein metabolism. See first line of summary, page 293 of Murase et al.

Since the reference is concerned with the presence or absence of hepatic triglyceride lipase on the surface of hepatic endothelial cells, which are not even in the gastrointestinal tract, the reference does not anticipate Applicant's claim 25, which requires in part that the "lipase regulates a biochemical process in the gastro-intestinal tract." According to the Murase et al reference, the physiological function of the enzyme in lipoprotein metabolism is still unclear. Thus, the Murase et al. reference does not disclose that HTGL regulates biochemical processes in the gastrointestinal tract, nor does it disclose that this specific enzyme occurs in the gastrointestinal tract.

In fact, the Murase et al reference involves a laboratory investigation into plasma lipoprotein metabolism wherein the intravenous administration of HTGL led to an increase in plasma of the lipids cholesterol, phospholipids and protein

concentrations. The reference concludes with a statement that "[i]n summary, the present study indicates that HTGL mediates the removal of remnant lipoproteins by the liver." This is the opposite of the desired effect of Applicant's invention regarding inhibiting pancreatic lipase.

The Applicant amended claim 25 by specifying that the lipase is -- orally -- administered to the animal, in order to further distinguish claim 25 from the Murase et al reference, wherein lipase is administered only intravenously.

35 U.S.C. 103

The Examiner rejected claims 1-4, 8, 11, 14, and 17-22 under 35 U.S.C. § 103 as being unpatentable over Hadvary et al., 4,598,089, in view of Moloney (Livestock Production Science, 1995, 42:239-245), Flint (Proceedings of the Nutrition Society, 1992, 51:433-439), Ohkaru et al (Clin. Chim Acta (1989) 182:295-300) or JP 02150294, Coleman, U.S. Patent No. 5,585,098, Tokoro, U.S. Patent No. 5,080,895. According to the Examiner, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody of Ohkaru et al. or JP 02140294 [sic. JP 02150294] for the tetrahydrolipstatin of Hadvary et al., U.S. Patent No. 4,598,089, in view of the teachings of Moloney and Flint. In support of this rejection, the Examiner argues that both molecules, namely the antibody of Ohkaru et al or JP 02140294 [sic. JP 02150294], and the tetrahydrolipstatin of Hadvary et al., U.S. Patent No.

4,598,089, are inhibitors of pancreatic lipase; Moloney suggests the identification of specific antigenic determinants to be used in immunological methods to decrease fat content in meat; and Flint suggests the immunoneutralization of gastrointestinal substances having direct lipogenic effects on adipose tissues for immunomodulation of adiposity. Also, because both Moloney and Flint, according to the Examiner, teach the importance of immunological manipulation of fat deposition and adiposity.

The Examiner argues a second ground of obviousness, namely that it would have been prima facie obvious to administer avian antibodies against lipase produced from animal antigens (based on the method of Hadvary et al., U.S. Patent No. 4,598,089 being performed in animals), produced in eggs, and in various feed forms (based on Coleman U.S. Patent No. 5,585,098 teaching successful oral administration of chicken yolk immunoglobulins to cattle in feed; and Tokoro, U.S. Patent No. 5,080,895 teaching the use of antibodies derived from avians in feed substances). In support of this obviousness rejection, the Examiner argues that Tokoro, U.S. Patent No. 5,080,895 teaches that oral administration of avian antibodies was desirable in the art.

Finally, the Examiner argues that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to freeze dry the antibodies into powder form because lyophilized reagents store well. In support of this rejection, the Examiner argues that one of ordinary skill in the art would have been motivated to freeze dry the antibodies

into a powder form so as to insure a ready supply of intact, stable antibodies.

The Applicant respectfully traverses the Examiner's obviousness rejections. There is no motivation to one of ordinary skill in the art to combine the teachings of these several references in the manner proposed in order to arrive at the Applicant's claimed invention, and given the long period of time between the publication dates of some of the references and the Applicant's invention, if the Applicant's invention were indeed obvious, one would certainly have combined the teachings of the references in the proposed manner prior to the Applicant. These facts support the non-obviousness of the Applicant's invention. The lack of motivation to one of ordinary skill in the art to combine the teachings of the references as proposed by the Examiner can be demonstrated by considering each of the references in turn.

First, the Hadvary et al. reference, published in 1986, which is the only reference cited by the Examiner dealing with the use of a lipase blocking agent in animals or humans, however, the reference does not make any mention of antibodies used for such a purpose. If the Examiner were correct in the argument that because both antibodies taught by Ohkaru et al or JP 02150294, and the tetrahydrolipstatin of Hadvary et al. are molecules that are inhibitors of pancreatic lipase, it would have been obvious to substitute the antibodies for the tetrahydrolipstatin, then the Applicant respectfully submits that

one of ordinary skill in the art would certainly have made such a substitution in the 12 years that have passed since the Hadvary et al. patent issued.

In fact, one of ordinary skill in the art looking at Hadvary et al. would be directed away from making such a substitution because the subject compounds of Hadvary et al., namely leucine derivatives, are produced from streptomyces strains found in soil which are subjected to fermentation. Although they are active against pancreatic lipase in animals, the compounds do not have the same mode of action as antibodies. The Applicant's invention works via an antigen-antibody reaction, whereas the compounds of Hadvary et al. do not participate in such a reaction.

In further support of the Applicant's view that the Examiner's election requirement in Section 15 of the March 30, 1998 Office Action is improper, the Applicant notes that claim 6 of Hadvary et al. claims an oral unit dosage form that is "a tablet, dragee, capsule, solution, emulsion or suspension". Thus, it is permissible to have in a single patent multiple forms of orally ingestible media by which to transfer a substance to an animal.

Next, the reference JP 02150294, published in 1990, deals with monoclonal antibodies and their use in methods for measurement and testing in immunopathology, specifically for measuring pancreatic lipase in disease where more than one antibody is employed. There is no suggestion or disclosure of

the production of useable antibodies. The reference is concerned with preparing a reagent for use in a laboratory, not with the nutrition or the treatment of obesity.

The Applicant respectfully submits that the JP 02150294 reference relates to non-analogous art, and would not be referred to by one of ordinary skill in the art who was concerned with overcoming the problems faced by the Applicant. The Applicant fails to see a motivation on the part of a person of ordinary skill seeking to find an oral method for reducing fat deposition, to look to the development of a laboratory test disclosed in the Japanese reference or to combine the teachings of the Japanese reference with the Hadvarey et al. patent, as proposed by the Examiner.

Ohkaru et al, a full copy of which is enclosed, was concerned with the same goal as the authors of JP 02150294, namely the production of an immunopathology or immunoassay test for measuring serum lipase. It is respectfully submitted that if indeed the Applicant's claimed invention were obvious, it would have certainly been unveiled by the groups of authors (those of the Ohkaru et al. reference and those of the JP 02150294 reference) actively researching in this area based on the earlier-issued Hadvary patent to develop an antibody specifically for treating obesity by controlling fat deposition. That almost ten years passed before Applicant's invention, despite a long-felt need to find an effective method of treating obesity, demonstrates the non-obviousness of Applicant's invention.

Tokoro, U.S. Patent No. 5,080,895, discloses the oral administration of a substance containing a specific antibody produced in eggs laid by hens. The antibody is intended for use against infectious disease, rather than for nutritional or dietary use. The Applicant respectfully submits that it would not have been obvious to one of ordinary skill in the art to look to the teachings of Tokoro regarding the oral administration of antibodies against infectious diseases, and combine such teachings with the use of antibodies against lipase in animals according to the teachings of Hadvery et al, in order to arrive at Applicant's claimed invention. If it were obvious, then such a combination would have been made between the time of application of Tokoro and the Applicant's claimed invention.

The Flint reference was cited by the Applicant in the background section of the present application. It discloses reducing fat accumulation in animals by passively administering antibodies against adipocyte plasma membrane, not lipase, and by immunizing against growth hormone. The antibodies do not inhibit lipase in the gastrointestinal tract. Under the heading "immuno-enhancement", the Flint reference discusses interactions with antibodies which might be applied to various actions of growth hormone, but not to reduced fat deposition. The Applicant's invention is intended and claimed for oral administration, whereas the Flint reference discloses only passive administration.

Under the heading "immuno-cytotoxicity," the Flint reference does disclose the use of antibodies for reducing fat deposition by considering adipocytes as invading organisms and producing antibodies capable of binding to and destroying them. However, the results of the method disclosed showed that although adipocytes were reduced, the method led to increased protein deposition, and the subject test animals gained, rather than lost weight. The Flint reference, which appears to the Applicant to be a reference prepared by one of superior skill in the art, fails to contemplate the direct administration of an antibody to humans, and there is no suggestion in any of the references cited by the Examiner to motivate one of ordinary skill to combine the references with the teachings of Flint for the purpose of producing an anti-lipase antibody for oral administration.

Moloney, which was published three years after the Flint reference, further demonstrates the non-obviousness of Applicant's invention because it discusses the continuing problem of controlling or reducing fat deposition in animals. Despite the numerous references demonstrating substantial work in the field of active and passive immunization using antibodies, as demonstrated by the several references cited by the Examiner, none of the references demonstrates the successful production of an anti-lipase antibody for oral administration to humans and animals, or even hinted that this was an avenue worthy of further study. The Applicant, however, moved in a different direction

than the teachings of the prior art, and arrived at an unexpected result, particularly unexpected in light of the weight gaining results obtained by the Flint study, and arrived at a patentably distinct invention.

Coleman, U.S. Patent No. 5,585,098, is similar to Tokoro, in that it teaches an active immunizing process using bacteria as the immunizing agent. Coleman does not separate the antibodies from the egg yolk, stating that it is unnecessary to do so. Coleman's only use of antibodies produced from egg yolks of hens is to control noxious agents, whether bacterial, fungal, protozoal, viral, toxins or inflammatory mediators. There is no suggestion or teaching of employing antibodies against active enzymes occurring in normal physiological processes in general, or specifically controlling such processes in the gastrointestinal tract. Indeed, the invention of Coleman is directed away from the gastrointestinal tract and, rather, is directed to a site remote therefrom, namely the mammary glands of cows.

The Applicant fails to see how it would have been obvious by looking to Coleman for one of ordinary skill in the art to orally administer avian antibodies to mammals to inhibit pancreatic lipase, where such antibodies were produced by hens, when no one made such a combination in the years intervening the Tokoro and Coleman patents, nor was the combination anywhere disclosed prior to the present application. It is respectfully submitted that the Examiner appears to be applying impermissible

hindsight reconstruction in order to reject the claims of the present application.

## CONCLUSION

In view of the foregoing, it is respectfully submitted that the claims pending in the present application, as amended, are now in condition for allowance. The Examiner's reconsideration and favorable action are respectfully requested.

Respectfully submitted,

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